Mesh inlay, mesh kit or native tissue repair for women having repeat anterior or posterior prolapse surgery

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ABSTRACT

Objective

To compare standard (native tissue) repair against synthetic mesh inlays or mesh kits.

Design

Randomised controlled trial.

Setting

33 UK hospitals.

Population

Women having surgery for recurrent prolapse.

Methods

Women recruited using remote randomisation.

Main Outcome Measures

Prolapse symptoms, condition specific quality-of-life and serious adverse effects.

Results

Mean Pelvic Organ Prolapse Symptom Score at 1 year was similar for each comparison (standard 6.6 versus mesh inlay 6.1, mean difference (MD) –0.41, 95% CI [–2.92 to 2.11]: standard 6.6 versus mesh kit 5.9, MD –1.21 [–4.13 to 1.72]) but the confidence intervals did not exclude a minimally important clinical difference. There was no evidence of difference in any other outcome measure at 1 or 2 years. Serious adverse events, excluding mesh exposure, were similar at 1 year (standard 7/55 [13%] versus mesh inlay 5/52 [10%], risk ratio [RR] 1.05, [0.66 to 1.68]: standard 3/25 [12%] versus mesh kit 3/46 [7%], RR 0.49, [0.11 to 2.16]). Cumulative mesh exposure rates over 2 years were 7/52 (13%) in the mesh inlay arm, of whom four women required surgical revision; and 4/46 in the mesh kit arm (9%) of whom two required surgical revision.

Conclusions

We did not find evidence of a difference in terms of prolapse symptoms from the use of mesh inlays or mesh kits in women undergoing repeat prolapse surgery. Although the sample size was too small to be conclusive, the results provide a substantive contribution to future meta-analysis.

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Trial registration

Controlled-Trials.com number ISRCTN60695184

Keywords

Pelvic organ prolapse; repeat surgery; randomised controlled trial; synthetic mesh

Tweetable abstract (110 characters)

Not enough evidence to support use of synthetic mesh inlay or mesh kits for repeat prolapse surgery

INTRODUCTION

Mesh use for prolapse surgery is controversial. Government policy is changing in the light of increased evidence of adverse effects.[1] In women having a first prolapse repair, our own multicentre randomised controlled trial (RCT) PROSPECT set in the UK[2] demonstrated in the short term, at two years, that more than 30% of women still reported either 'something coming down' or had anatomical prolapse extending beyond the hymen, irrespective of the use of mesh inlay or biological graft to reinforce the surgery. As a result of the findings from this trial, augmentation is no longer recommended for a first repair.[1]

However, Olsen et al showed that 30% of women who have had one prolapse or incontinence operation required at least one more procedure, and the time intervals between repeat procedures decreased with each successive repair.[3] This study failed to differentiate between repeat surgery for a recurrence in the same compartment and primary surgery for a de novo prolapse in another compartment, or new continence procedures.[4] Nevertheless, Olsen's study suggests that a third of women would eventually undergo at least one more procedure and some would require a third or fourth one.[3]

Our study was preceded by priority assessment based on the relevant Cochrane review[5] and an Interventional Procedures review which investigated the use of mesh for women having anterior and/or posterior vaginal wall prolapse surgery.[6] These and other findings were presented to the Interventional Procedures Advisory Committee (IPAC) in January 2008 and their guidance published.[7] The committee recommended that mesh should be used only under special arrangements for clinical governance, consent and audit or research: hence the PROSPECT Study was funded to fill the evidence gap.

We therefore compared, in an RCT, the effect of mesh inlay or mesh kit with native tissue repairs in women who had already experienced at least one failed previous prolapse repair in the same compartment.

We focused on those high-risk women whose specific compartment prolapse surgery had already failed in order to try to reduce the chance that they would require further prolapse surgery. After consultation with gynaecologists and experts from specialist societies, we chose to compare mesh kits as well as mesh inlays with standard (native tissue) repairs, based on the scarcity of data about the safety and efficacy of mesh kits but their perceived potential to provide better support due to their method of insertion.

METHODS

Participants

Women listed for transvaginal repair of an anterior and/or posterior prolapse were eligible if at least one of the compartments requiring surgery had been repaired previously. Women could have concomitant uterine, vault, or continence surgery. Women under the care of 59 gynaecologists from 33 UK centres were enrolled into the trial between January 2010 and August 2013. All women provided written informed consent. The study was funded by the National Institute for Health Research Health Technology Assessment Programme (Project Number 07/60/18). The funder (through their peer review and funding board review process) approved the study proposal but had no role in the collection, analysis, or interpretation of data, or writing of the report.

Randomisation

A remote web-based computer-generated randomisation system at the Centre for Healthcare Randomised Trials (CHaRT, University of Aberdeen, UK) was used for group allocation. We report two trials: the Mesh Inlay Trial compared standard (native tissue) repair to mesh inlay; and the Mesh Kit Trial compared standard repair to mesh kit. Not all gynaecologists offered all treatment options due to preference or locally available resources. Therefore, women were randomised within three strata: Stratum A included women randomised to one of all three treatment options, standard repair, mesh inlay, or mesh kit (in a 1:1:2 ratio); Stratum B compared standard repair with mesh inlay (in a 1:1 ratio); and Stratum C compared standard repair with mesh kit (in a 1:2 ratio). Randomisation was unbalanced in the Mesh Kit Trial in favour of mesh kits to account for the number of surgeons who were trained in their use to ensure adequate numbers in the groups. Because the analyses were carried out separately for each trial, data from some women in the standard repair group from Stratum A were included in both trials.

The minimisation algorithm included: age (<60 years or $\geq$60); planned prolapse repair (anterior, posterior, or both); planned concomitant urinary continence procedure or not; planned concomitant upper vaginal prolapse procedure or not; and operating surgeon.

Further details of participants, masking and interventions are provided as online Supplementary Information.

Outcomes

Women were followed up at six months, and one and two years after surgery by postal questionnaire, and were clinically examined at one year.[9]

We used a wide and comprehensive panel of validated core outcomes relevant to women, focusing primarily on women's symptoms. These were based on internationally-agreed terminology and recommended core outcomes.[4]

The primary outcome was women's report of prolapse symptoms at one year after surgery using the Pelvic Organ Prolapse Symptom Score (POP-SS), a validated measure which has been shown to be sensitive to change after treatment.[10] The POP-SS contains items relating to frequency of seven prolapse symptoms in the previous four weeks: each item is scored from 0 (never) to 4 (all of the time): the total score ranges from 0 to 28.

Secondary outcomes included prolapse-specific quality-of-life measured using a visual analogue scale (VAS) and generic quality of life based on the EQ-5D-3L,[11] and an assessment of overall global improvement in symptoms (PGI-I).[12] Bladder, bowel, and sexual function were measured using validated or adapted International Consultation on Incontinence Questionnaires (ICIQ).[13] Objective measurement of prolapse stage utilised the POP-Q system.[9]

Adverse events, need for readmission/further treatment for adverse effects, or prolapse recurrence were reported by surgeons or women, and verified by Study Office staff from a second source when possible. Adverse events and complications of surgery were recorded using the IUGA/ICS complications classification which includes type, severity, time of occurrence, and site.[14,15] Serious adverse events were defined using standard classification.[16]

All definitions are in keeping with the recommendations of IUGA, ICS, and ICI.[4,13-15,17] The full Protocol is available on the funders' website.[18]

Statistical analysis

The main analysis was conducted on an intention-to-treat basis (whereby women with observed outcome data remained in their allocated group for). We did not follow up randomised women who did not receive any surgery. We made two comparisons: standard repair versus mesh inlay (Mesh Inlay Trial, data from women in Strata A and B) and standard repair versus mesh kit (Mesh Kit Trial, from Strata A and C) (Figure S1). Study analyses were conducted according to a prespecified statistical analysis plan, using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

All outcome measures were presented as summaries using descriptive statistics (mean and standard deviation for continuous measures, and proportion for ordinal and dichotomous measures) and comparisons between randomised groups were analysed separately at six months and one and two years using generalised linear models. Models were adjusted for minimisation covariates, baseline measures where appropriate, and randomisation stratum. Continuous outcomes were analysed using linear mixed models with surgeon fitted as a random effect. POP-Q stage and PGI-I were analysed using ordinal logistic regression (proportional odds models with cumulative logits). Dichotomous outcomes were analysed using log-binomial regression. Estimates of treatment effect size were mean differences in the linear mixed models (including the analysis of the POP-SS), odds ratios in the ordinal models, and risk ratios in the binary models. For all estimates, 95% confidence intervals were calculated.

Sample size

Women were recruited opportunistically alongside those having a primary repair.[2] We expected, based on the assumption that 30% of women requiring an anterior and/or posterior repair would receive a secondary or subsequent operation,[3] that approximately 1240 women having secondary surgery would be available during the recruitment period for the primary trial.[2] Of those available, it was estimated that 50% (620 women) would agree to be randomised.

Pilot data indicated that women having secondary repairs had worse symptoms at baseline than those having their first repair (unpublished data)[19]. We considered it biologically plausible that these women might show a larger benefit from surgical treatment than women having their first repair. We therefore calculated that, with an expected sample size of 620, it would be possible to detect, with 90% power and alpha equal to 0.025, a standardised effect size of 0.38, which equates to three points on the POP-SS scale (assuming a standard deviation of 8 units).

RESULTS

Between January 2009 and August 2013, 396 women were found to have recurrent prolapse of the same compartment and therefore potentially eligible for this trial. However, only 155 (39%) agreed to be randomised, of whom 154 were included in the analyses.[8]

Baseline characteristics and intervention received

The flow of women through the study is shown in the CONSORT diagram (Figure 1) in line with recommendations of the Consolidated Standards of Reporting Trials.[20] Women in the randomised

groups were comparable at baseline and all were symptomatic based on at least one symptom on the POP-SS (Table S1). Two women did not receive surgery (Figure 1). Most women received their planned surgery (Figure 1).

In the standard repair group, more women (27% in the Mesh Inlay Trial and 20% in the Mesh Kit Trial) had a combined anterior / posterior repair than in the other two groups (synthetic mesh inlay 14% and mesh kit 13%) (Table S2). Concomitant surgery included vaginal hysterectomy which occurred in 7%/12% (respectively) of the standard repair groups, 8% with synthetic mesh inlay and 9% with mesh kit. A concomitant vault repair was more common in the native tissue group (25%/28%) compared to 10% in mesh inlay group and 13% in the mesh kit group. Finally, vaginal concomitant continence procedures were performed in 7%/8% of the native tissue repairs, in 4% of the mesh inlays and none were performed with mesh kits.

Clinical symptoms and quality of life at follow up (Table 1 and Tables S3, S4)

Women's report of prolapse symptoms (POP-SS), was less than half of the preoperative level (mean score before surgery 14.4 (SD 5.4), at six months 5.9 (5.7), at one year 6.3 (6.0), at two years 5.3 (5.3)). The improvement at one year was maintained at two years, in respect of all the prolapse and quality of life outcomes measured.

In the Mesh Inlay Trial, the mean difference (MD) in the POP-SS score at one year for standard repair (Mean 6.6, SD 6.0) versus synthetic mesh inlay (Mean 6.1, SD 6.4), based on combined data from women in Stratum A (three way randomisation) and Stratum B (two way randomisation), was -0.41 [95% CI -2.92 to 2.11].

In the Mesh Kit Trial, the MD in the POP-SS score at one year for standard repair (Mean 6.6, SD 5.5) versus mesh kit (Mean 5.9, SD 5.3), based on combined data from women in Stratum A (three way randomisation) and Stratum C (two way randomisation), was -1.21 [95% CI -4.13 to 1.72].

At two years, the study found that women having a mesh kit had a better generic QoL score, measured with EQ-5D-3L, than those who had a standard repair (MD 0.13 [95% CI 0.02 to 0.25: P=0.025; Table 1).

The other key symptoms of pelvic floor dysfunction, including urinary, faecal, vaginal and sexual symptoms are presented in Table 1 and Table S4. While there was a decrease in the proportion of women with severe urinary incontinence after surgery, there was no difference between the randomised groups in either the Mesh Inlay Trial or the Mesh Kit Trial in respect of any of the urinary outcomes measured. Frequency of bowel movement and constipation were largely unchanged after prolapse surgery. There were no differences between the randomised groups in respect of any of the bowel outcomes measured.

Many women reported improvements in their vaginal and sexual function outcomes after surgery: this was evident in a reduction of the ICI-Q Vaginal Symptoms score (Table 1). After surgery, fewer women cited prolapse symptoms as a reason for not having a sex life (around 35% before surgery, versus around 10% after). Four women had severe dyspareunia at one year (Mesh Inlay group = 3, Mesh Kit group = 1), but only one at two years (Mesh Inlay group). However, there were no statistically significant differences between the randomised groups in respect of any of the vaginal or sexual symptom outcomes measured.[8]

Satisfaction with treatment

Most women reported that their prolapse symptoms were very much or much better than before surgery, with no statistically significant differences between the groups in either trial (Table S4).

Objective outcomes

At one year, 83% of women attended for clinical review. Objective measurement showed improvement in each of the three prolapse compartments. The proportion of women with the leading prolapse edge beyond the hymen (POPQ >0cm) reduced substantially. In the Mesh Inlay Trial, the difference between groups based on clinician's estimates of stage was RR 0.75, 95% CI 0.33 to 1.68, p=0.479, and the proportion with more severe objective prolapse defined as 'leading edge of the prolapse at >0cm beyond the hymen on POP-Q' was 14% in each group (RR 0.59, 95% CI 0.18 to 1.92, p=0.380 (Table 2).

In the Mesh Kit Trial, women who had a standard repair were more likely to have prolapse than those who were randomised to mesh kit based on clinician's estimates of all stages (RR 0.24, 95% CI 0.07 to 0.83, p=0.024; (Table 2). However, for more severe objective prolapse (defined as above), 3/18 (17%) of standard repair women had residual prolapse compared with none of 35 women after a mesh kit procedure.

Readmission, adverse effects and further treatment

Five women were readmitted in the first six months after surgery (Standard group = 2, Mesh Inlay group = 3) (Table 3). Two subsequent readmissions were for revision of prolapse surgery (Fenton's operation), one in the Mesh Kit group and one in the Mesh Inlay group.

Individual serious adverse events were rare, the most common being infection, pain and urinary retention (Table S5). In the first year, the number of women with serious non-mesh adverse events were: Mesh Inlay Trial: standard 7/55, 12.7% versus mesh inlay 5/52, 9.6%, RR 1.05, 95% CI 0.66 to 1.68, p=0.831; Mesh Kit Trial: standard 3/25, 12.0% versus mesh kit 3/46, 6.5%, RR 0.49, 95% CI 0.11 to 2.16, p=0.345. No women experienced cystotomies or bladder perforations during either mesh insertion or native tissue repair. One woman, in the mesh kit arm, required a blood transfusion. Non-serious adverse events were also rare (Table S6).

In the first two years, 7/52 women had vaginal mesh exposure in the mesh inlay arm (13%) of whom four required surgical revision; and 4/46 women had vaginal mesh exposure in the mesh kit arm (8%) of whom two needed surgical revision. Hence in total six women needed further surgery to address an area of mesh exposure (all but one less than $1cm^2$) by two years after surgery. There were no reports of mesh perforation of the bladder or bowel at insertion but one woman in the Mesh Inlay Trial experienced a bowel perforation during mesh removal. The other mesh exposures were managed conservatively by observation, topical oestrogens or cautery.

At two years after surgery, around one in five women who had a standard repair required further treatment for prolapse compared to 11% who had a mesh inlay and 5% who had a mesh kit (Table 3): however, there was no statistical difference between the randomised groups.

DISCUSSION

Main findings

There were no statistically significant differences at one year in the primary clinical outcomes after prolapse surgery using native tissue, polypropylene non-absorbable mesh or a mesh kit to reinforce the repair in either Trial. The uncertainty around this finding is reflected in the wide confidence intervals around the primary outcome, (POP-SS) at one year: RR -0.41 [95% CI -2.92 to 2.11] in the Mesh Inlay Trial and RR -1.21 [95% CI -4.13 to 1.72] in the Mesh Kit Trial. Women in the Mesh Kit Trial were less likely to have prolapse beyond Stage 2 at one year and had a higher (better) EQ-5D-3L score at two years. However, these may have been chance findings

and their clinical significance is uncertain as there were no differences in any other subjective outcomes between the randomised groups at any time point.

The overall incidence of non-mesh related serious adverse events was around 10%, and were primarily pain, infection and urinary retention. As women could only have a mesh-related complication if they received mesh, the total numbers for this outcome are small, with six women needing further surgery to address mesh exposure.

Strengths and Limitations

PROSPECT is rare in being one of the few RCTs in the field to distinguish between primary and secondary surgery. Unfortunately our secondary trials on their own did not attain sufficient power to detect a difference. In future, studies should report prolapse surgery trials using the subgroups of Primary and Secondary (the latter defined as 'repeat surgery in the same compartment').

Another strength was the pragmatic reflection of actual practice in the UK. We included surgeons from a large number of hospital settings. Surgeons were not all able to randomise between all three options, but the analysis by strata accommodated this.

Our secure and effective randomisation programme ensured that women were comparable at baseline and that concomitant surgery and other confounding variables were accounted for. We used validated outcome measures to measure women's symptoms of pelvic floor dysfunction. We captured a wide range of adverse effects, and made efforts to verify these from alternative sources when possible. Essential missing data were actively sought from the women. Participants, outcome assessors and data entry clerks were blinded to randomisation as far as possible.

Limitations of our study should be acknowledged. The complex design of the study (with three interventions across three strata) generated multiple comparisons, particularly across the secondary outcomes, so care must be taken not to over interpret the results as it is likely that some differences may have occurred by chance.

Furthermore, we identified fewer women than expected (396 rather than 1240) because of our more rigorous definition of repeat surgery (same compartment rather than any compartment, 30%.)[1] In addition, fewer women than expected were randomised (39% rather than 50%): this was more likely to be due to a clinical decision rather than the women's choice (54% versus

39%). This resulted in fewer women than estimated (155 rather than 620) being randomised. Thus, we were not able to recruit to the sample size which would have given us enough power to identify a difference of three points on the POP-SS.

We and other researchers have suggested that prolapse beyond the hymen (>0cm on POP-Q), is a sign of severe objective failure.[21] However we recognise that women with worse anatomical findings may not have symptoms and, vice versa, women with objective 'cure' may still have prolapse symptoms.

Longer follow up is required: the average time to a repeat operation (in any compartment) is around 12 years.[1] While we did not identify differences in the repeat surgery rate between the groups, it is likely that two years is too short a time scale to provide a definitive answer. Both the natural history of prolapse and the long-term ongoing tissue interactions with polypropylene indicate that it is important that trials pursue longer term follow up of outcomes and complications, ideally over 12 years.[3] We have commenced follow up of the PROSPECT women for at least six years after surgery, and also plan electronic data linkage to capture outcomes from non-responders about further admission for prolapse surgery.

Interpretation (in light of other evidence)

The most recent Cochrane review (Maher 2016)[22] identified 37 trials of mesh or graft, in women having anterior, posterior or apical prolapse surgery. Only two of those RCTs published separate data from women having repeat surgery for recurrent anterior or posterior prolapse[23,24] although most trials included some such women. Both relevant RCTs compared native tissue repair to a mesh kit (Prolift ® Gynaecare, inserted with trochars, which is no longer available). Altman reported only a composite failure rate at one year in 53 women (20/25 versus 14/28).[23] Withagen reported long term prolapse symptoms at seven years in up to 142 women (sensation of bulge at seven years: 17/76 with native tissue versus 14/66 with mesh kit).[24] While anatomical failure rates were less in the mesh group (47/67 versus 28/53 at 7 years), there was little difference in the further prolapse surgery rate (11/69 versus 14/56). The mesh exposure rate in the mesh kit group (42% at seven years) was high and 54% were symptomatic, while a third of the women required surgical revision. Neither trial was conclusive.

Meta-analysis of the PROSPECT data with the two trials examining mesh kits showed that more women had prolapse symptoms with native tissue (68%) versus 42% with mesh kits (RR 1.56, 95% CI 1.11 to 2.18) in the first year, but this difference did not persist in the longer term (23%

versus 27%: RR 0.92, 95% CI 0.55 to 1.52). While more women had persistent objective prolapse at one year (40% versus 7%, RR 4.97, 95% CI 2.52 to 9.81) this was not reflected in repeat prolapse surgery rates (17% versus 18%, RR 0.85, 95% CI 0.46 to 1.54) at up to 7 years' follow up. Four women of 52 required surgery for mesh exposure after a mesh inlay, and 9/99 women after a mesh kit, although many mesh exposures were small and asymptomatic.

PROSPECT was the only trial to compare native tissue repairs with synthetic mesh inlays.

In any case, it is unlikely that further trials of mesh will be conducted, in the light of increased evidence of adverse effects.[1]

CONCLUSIONS

Based on the evidence available in this trial, we are unable to say whether or not a mesh inlay or a mesh kit confers more benefit to women having a repeat prolapse repair than native tissue surgery in the first two years after surgery. Some women required an additional surgical procedure to remove exposed mesh, which may be considered to be an unnecessary risk. However, long term follow up may show whether or not the excess risks are offset by a potential decrease in the need for repeat surgery, with its associated higher risks, in the future.

PROSPECT is rare in being one of the few RCTs to rigorously distinguish between primary and repeat surgery. We would strongly encourage future studies to take our approach. Although our trial did not have sufficient power to demonstrate a statistical difference, the information is available for meta-analysis with other trials.[8] Further long-term follow-up will ultimately determine whether the use of synthetic mesh in vaginal prolapse repair provides any long-term benefits in women whose prolapse surgery has already failed at least once. Large international data sets will be required to make true progress in this field.

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Contributions of authors

CG, CH, KC, RF, AS, SH, IM, AM, GM[c], GMac and JN designed the study. CG, SB and AM managed the study with support, input and oversight from CH, KC, RF, AS, SH, IM, MK, GM[c], GMac and JN. AE, MK and DB analysed the data, which were interpreted by all other authors. IM provided patient and pubic perspective at all stages of the study. CG, SB, AE and FR wrote the first draft of the manuscript which was reviewed, modified and approved by all other authors. All the authors vouch for the accuracy and completeness of the data reported and for the fidelity of the study to the protocol.

All members of the local recruitment teams and gynaecologists at the 33 recruiting centres are members of the PROSPECT STUDY Group:

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Study Oversight

The PROSPECT study was overseen by an independent Trial Steering Committee (Henry Kitchener [Chair], Ranee Thakar (Clinician), Pamela Warner (Statistician), Trish Emerson (Patient Representative, 2012 – present), Catherine Rodger (Patient Representative, 2010 – 2012) and an independent Data Monitoring Committee (James Neilson [Chair], Lucia Dolan (Clinician), Paula Williamson (Statistician), Gill Gyte, Patient Representative,).

Disclaimer

The views and opinions expressed herein are those of the authors and do not necessarily reflect those of the Health Technology Assessment Programme, the National Institute of Health Research, the National Health Service or the Department of Health.

Declaration of interests

Mr. Elders reports that his institution (Glasgow Caledonian University) received payment from the University of Aberdeen for statistical analysis undertaken by him. Prof. Norrie reports grants from University of Aberdeen, during the conduct of the study; and Norrie declares grants from University of Edinburgh, during the conduct of the study; and Membership of the following NIHR boards: CPR decision making committee; HTA Commissioning Board; HTA Commissioning Sub-Board (EOI); HTA Funding Boards Policy Group; HTA General Board; HTA Post-Board funding teleconference; NIHR CTU Standing Advisory Committee; NIHR HTA & EME Editorial Board; Pre-exposure Prophylaxis Impact Review Panel. All other authors report no conflict of interest. Completed disclosure of interest forms are available to view online as supporting information.

Details of ethics approval

PROSPECT was approved by the North of Scotland Research Ethics Committee (NOSRES) on 7th July 2009 (REC reference number 09/SO802/56).

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Table 1a Clinical symptoms and quality of life outcomes at one and two years: Mesh Inlay Trial.

	Mesh Inlay Trial: Standard v Synthetic Mesh Inlay				
	Standard	**Mesh Inlay**	**Est·**	**95% CI**	**p-value**
1-year outcomes:	N=49	N=44			
POP-SS at 1 year	6·6 (6·0) 49	6·1 (6·4) 44	-0·41	-2·92 to 2·11	0·747
Prolapse-related QoL score [1]	2·5 (2·9) 47	3·0 (3·4) 44	0·43	-0·90 to 1·75	0·522
Symptomatic prolapse [2]	81·6% 40/49	88·6% 39/44	1·05	0·82 to 1·33	0·714
Women with any report of SCD [3]	44·9% 22/49	40·9% 18/44	0·91	0·58 to 1·43	0·680
Urinary incontinence (severe) [4]	2·2% 1/46	12·8% 5/39	5·52	0·68 to 44·77	0·110
Faecal incontinence (any) [5]	26·1% 12/46	43·6% 17/39	1·41	0·84 to 2·35	0·190
ICI Vaginal Symptoms Score	8·3 (7·4) 44	7·9 (8·6) 37	-1·29	-4·99 to 2·42	0·487
Dyspareunia (severe) [6]	0·0% 0/18	13·0% 3/23	n/a	n/a	n/a
EQ-5D-3L score at 1 year	0·74 (0·30) 50	0·83 (0·22) 43	0·03	-0·07 to 0·14	0·519
PGI-I at one year [7]	76·7% 33/43	81·6% 31/38	1·18	0·47 to 2·95	0·731
2-year outcomes:	N=43	N=39			
POP-SS at 2 years	4·8 (5·0) 43	5·4 (5·5) 39	0·58	-1·68 to 2·84	0·607
Prolapse-related QoL score [1]	1·7 (2·4) 41	2·4 (2·7) 36	0·38	-0·84 to 1·60	0·529
Symptomatic prolapse [2]	83·7% 36/43	82·1% 32/39	1·00	0·80 to 1·24	0·981
Women with any report of SCD [3]	30·2% 13/43	25·6% 10/39	0·78	0·38 to 1·60	0·497
Urinary incontinence (severe) [4]	7·1% 3/42	10·3% 4/39	1·64	0·38 to 7·07	0·507
Faecal incontinence (any) [5]	27·9% 12/43	44·7% 17/38	1·35	0·74 to 2·47	0·326
ICI Vaginal Symptoms Score	7·3 (7·6) 39	7·9 (7·8) 37	-0·64	-4·56 to 3·28	0·742
Dyspareunia (severe) [6]	0·0% 0/15	4·5% 1/22	n/a	n/a	n/a
EQ-5D-3L score at 2 years	0·76 (0·29) 42	0·82 (0·19) 38	0·00	-0·11 to 0·11	0·975
PGI-I at two years [7]	81·0% 34/42	74·4% 29/39	1·01	0·41 to 2·49	0·974

Table 1b Clinical symptoms and quality of life outcomes at one and two years: Mesh Kit Trial.

	Mesh Kit Trial: Standard v Mesh Kit				
	Standard	**Mesh Kit**	**Est·**	**95% CI**	**p-value**
1-year outcomes:	N=21	N=44			
POP-SS at 1 year	6·6 (5·5) 21	5·9 (5·3) 44	-1·21	-4·13 to 1·72	0·408
Prolapse-related QoL score [3]	2·0 (2·6) 21	2·3 (2·8) 43	-0·31	-1·99 to 1·36	0·706
Symptomatic prolapse [1]	90·5% 19/21	86·4% 38/44	0·93	0·67 to 1·28	0·638
Women with any report of SCD [2]	57·1% 12/21	36·4% 16/44	0·57	0·29 to 1·10	0·094
Urinary incontinence (severe) [4]	0·0% 0/21	10·0% 4/40	n/a	n/a	n/a
Faecal incontinence (any) [5]	28·6% 6/21	39·0% 16/41	1·59	0·57 to 4·49	0·378
ICI Vaginal Symptoms Score	6·7 (6·0) 18	5·8 (4·8) 35	-2·82	-6·67 to 1·02	0·143
Dyspareunia (severe) [6]	0·0% 0/6	5·6% 1/18	n/a	n/a	n/a
EQ-5D-3L score at 1 year	0·79 (0·27) 22	0·83 (0·19) 41	0·05	-0·07 to 0·17	0·411
PGI-I at one year [7]	77·8% 14/18	87·2% 34/39	0·58	0·18 to 1·90	0·372
2-year outcomes:	N=20	N=39			
POP-SS at 2 years	3·9 (4·4) 20	5·4 (5·3) 39	0·65	-2·20 to 3·50	0·642
Prolapse-related QoL score [3]	1·5 (2·6) 18	2·5 (2·7) 37	0·32	-1·45 to 2·09	0·712
Symptomatic prolapse [1]	85·0% 17/20	76·9% 30/39	0·92	0·63 to 1·33	0·655
Women with any report of SCD [2]	25·0% 5/20	35·9% 14/39	1·17	0·47 to 2·87	0·739
Urinary incontinence (severe) [4]	5·0% 1/20	10·3% 4/39	1·58	0·20 to 12·48	0·663
Faecal incontinence (any) [5]	30·0% 6/20	38·5% 15/39	1·04	0·47 to 2·31	0·918
ICI Vaginal Symptoms Score	6·1 (6·2) 17	7·9 (7·4) 36	0·08	-4·91 to 5·08	0·973
Dyspareunia (severe) [6]	0·0% 0/6	0·0% 0/16	n/a	n/a	n/a
EQ-5D-3L score at 2 years	0·76 (0·29) 20	0·87 (0·14) 38	0·13	0·02 to 0·25	0·025
PGI-I at two years [7]	85·0% 17/20	89·5% 34/38	1·53	0·47 to 4·96	0·478

[1] Quality of life due to prolapse symptoms measured as 'overall interference of prolapse symptoms with everyday life' using a visual analogue scale (VAS); score range from 0 (not at all) to 10 (a great deal)

[2] Symptomatic defined as POP-SS > 0

[3] Women with any report of something coming down

[4] Severe urinary incontinence defined as ICIQ-SF score 13-21

[5] Faecal incontinence of solid or liquid stool: any = occasionally or more

[6] Severe dyspareunia defined as 'Do you have pain when you have sexual intercourse: 'a lot.' Denominators confined to sexually active women

[7] PGI-I Patient-Global impression of Improvement = very much or much better (versus a little better, no change, a little worse, much worse, very much worse). Effect sizes are odds ratios estimated from ordinal logistic regression·

Continuous variables presented as Mean (SD) N; dichotomous variables presented as % n N

Effect size:

For all negative continuous outcomes e.g. POP-SS: a positive effect size favours standard

For all positive continuous outcomes e.g. EQ5D: a positive effect size favours synthetic / mesh kit

For all negative dichotomous outcomes e.g. urinary incontinence: an effect size more than 1 favours standard

For all positive dichotomous outcomes e.g. prolapse better: an effect size more than 1 favours synthetic / mesh kit

Table 2 Objective measures of prolapse at one year.

	Mesh Inlay Trial					Mesh Kit Trial				
	Standard	**Mesh Inlay**	**Est·**	**95% CI**	**p-value**	**Standard**	**Mesh kit**	**Est·**	**95% CI**	**p-value**
One-year review	N=46	N=44				N=21	N=38			
POP-Q										
Ba	-1·4 (1·5) 42	-1·4 (1·4) 41	-0·22	-0·80 to 0·36	0·445	-1·2 (1·9) 19	-1·8 (1·0) 35	-0·74	-1·4 to -0·10	0·026
C	-5·6 (2·4) 41	-6·2 (1·5) 41	-0·61	-1·38 to 0·16	0·119	-5·1 (2·7) 18	-6·0 (1·8) 33	-0·65	-1·6 to 0·3	0·173
Bp	-1·8 (1·6) 41	-2·2 (1·1) 41	-0·49	-1·08 to 0·10	0·099	-1·9 (1·7) 18	-2·2 (0·8) 34	-0·38	-1·2 to 0·4	0·317
Tvl	7·7 (1·2) 43	7·9 (1·4) 42	0·09	-0·47 to 0·65	0·746	7·7 (1·0) 19	8·1 (1·2) 33	0·64	0·1 to 1·20	0·028
Overall POP-Q stage										
Stage 0	13·6% 6/44	7·0% 3/43	0·75	0·33 to 1·68	0·479	10·5% 2/19	14·3% 5/35	0·24	0·07 to 0·83	0·024
Stage 1	36·4% 16/44	44·2% 19/43				31·6% 6/19	45·7% 16/35			
Stage 2	40·9% 18/44	46·5% 20/43				42·1% 8/19	40·0% 14/35			
Stage 3	9·1% 4/44	2·3% 1/43				15·8% 3/19	0·0% 0/35			
Stage 4	0·0% 0/44	0·0% 0/43				0·0% 0/19	0·0% 0/35			
Stage 2b, 3 or 4 [1]	14·0% 6/43	14·0% 6/43	0·59	0·18 to 1·92	0·380	16·7% 3/18	0·0% 0/35	n/a	n/a	n/a

% n/N or mean (SD) N

1 Objective prolapse: stage 2b, 3, or 4, defined as leading edge beyond the hymen (>0 cm) when POP-Q data available.

Table 3 Readmission, adverse effects and further treatment

	Mesh Inlay Trial: Standard v Synthetic Mesh Inlay					Mesh Kit Trial: Standard v Mesh Kit				
	Standard	**Mesh Inlay**	**Est·**	**95% CI**	**p-value**	**Standard**	**Mesh Kit**	**Est·**	**95% CI**	**p-value**
	N=43	N=38				N=20	N=39			
Readmissions 0-6 months	4·0% 2/50[1]	6·4% 3/47[2]	1·76	0·30 to 10·37	0·532	0% 0/22	0% 0/43	n/a	n/a	n/a
Readmissions 6-12 months	0% 0/49	0% 0/44	n/a	n/a	n/a	0% 0/21	2·3% 1/44[3]	n/a	n/a	n/a
Readmissions 12-24 months	0% 0/43	2·6% 1/39[4]	n/a	n/a	n/a	0% 0/20	0% 0/39	n/a	n/a	n/a
Any serious adverse effects in 1st year (excluding mesh exposures)	12·7% 7/55	11·5% 6/52	0·87	0·32 to 2·35	0·777	12·0% 3/25	6·5% 3/46	0·49	0·11 to 2·16	0·345
Any serious adverse effects in 2nd year (excluding mesh exposures)	0% 0/55	0% 0/52	n/a	n/a	n/a	0% 0/25	4·3% 2/46	n/a	n/a	n/a
Any mesh exposure (cumulative by 2 years)	0% 0/55	13·5% 7/52	n/a	n/a	n/a	0·0% 0/25	8·7% 4/46	n/a	n/a	n/a
Surgical removal of mesh exposure (cumulative by 2 years)	0·0% 0/43	10.5% 4/38	n/a	n/a	n/a	0·0% 0/20	5.1% 2/39	n/a	n/a	n/a
New prolapse operation (any by 2 years)	14·0% 6/43	7·9% 3/38	0·49	0·14 to 1·82	0·290	20·0% 4/20	2·6% 1/39	0·13	0·02 to 1·12	0·063
Same compartment	11·6% 5/43	2·6% 1/38	0·22	0·03 to 1·83	0·162	15·0% 3/20	2·6% 1/39	0·28	0·03 to 2·92	0·285
Different compartment	2·3% 1/43	5·3% 2/38	1·74	0·16 to 18·79	0·647	5·0% 1/20	0·0% 0/39	n/a	n/a	n/a
Pessary (by 2 years)	7·0% 3/43	2·6% 1/38	0·43	0·05 to 3·85	0·450	5·0% 1/20	2·6% 1/39	0·56	0·04 to 8·28	0·673
Pessary or prolapse surgery combined (by 2 years)	18·6% 8/43	10·5% 4/38	0·45	0·15 to 1·40	0·170	20·0% 4/20	5·1% 2/39	0·27	0·05 to 1·33	0·107

Footnotes

1 Reasons for readmission (Standard; 0-6 months): infection (2)

2 Reasons for readmission (Synthetic; 0-6 months): retention (1), adhesions (1), constipation (1)

3 Reasons for readmission (Kit; 6-12m): Revision prolapse surgery (Fenton's) (1)

4 Reasons for readmission (Synthetic; 12-24m): Revision prolapse surgery (Fenton's) (1)

Women identified 4083

Ineligible 3687
Not screened 339
Ineligible/declined 655 [1]
Primary surgery 2478
Upper compartment only 215

Eligible women 396

Declined randomisation 241 [2]

RANDOMISED 155

Post randomisation exclusions [3]

INCLUDED IN ANALYSIS 154 [4]

	MESH INLAY TRIAL [5] **107**		**MESH KIT TRIAL** [5] **71**	
Treatment arm	**Standard 55**	**Mesh inlay 52**	**Standard 25**	**Mesh kit 46**
No surgery	**0 (0%)**	**1 (2%)**	**0 (0%)**	**1 (2%)**
Received surgery	**55 (100%)**	**51 (98%)**	**25 (100%)**	**45 (98%)**
Standard repair	**49 (89%)**	**9 (18%)**	**20 (80%)**	**4 (9%)**
Synthetic mesh	**2 (4%)**	**37 (73%)**	**1 (4%)**	**17 (16%)**
Mesh kit	**0 (0%)**	**2 (4%)**	**0 (0%)**	**31 (69%)**
Biological graft	**1 (2%)**	**0 (0%)**	**1 (4%)**	**1 (2%)**
Other surgery [6]	**3 (5%)**	**3 (6%)**	**3 (12%)**	**2 (4%)**
Baseline questionnaire	**54 (98%)**	**50 (96%)**	**24 (96%)**	**43 (93%)**
6 month questionnaire	**50 (91%)**	**47 (90%)**	**22 (88%)**	**43 (93%)**
Withdrawals within 6 months	**0 (0%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**
Deaths within 6 months	**0 (0%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**
12 month 1^0 outcome	**49 (89%)**	**44 (85%)**	**21 (84%)**	**44 (96%)**
12 month 2^0 outcome	**46 (84%)**	**39 (75%)**	**21 (84%)**	**41 (89%)**
12 month clinic assessment	**46 (84%)**	**44 (85%)**	**21 (84%)**	**38 (83%)**
Withdrawals within 12 months	**1 (2%)**	**0 (0%)**	**0 (0%)**	**0 (0%)**
Deaths within 12 months	**1 (2%)**	**0 (0%)**	**1 (4%)**	**1 (0%)**
24 month questionnaire	**43 (78%)**	**39 (75%)**	**20 (80%)**	**39 (85%)**
Withdrawals within 24 months	**1 (2%)**	**3 (6%)**	**0 (0%)**	**2 (4%)**
Deaths within 24 months	**1 (2%)**	**0 (0%)**	**1 (4%)**	**0 (0%)**

Figure 1 CONSORT Diagram.

Footnotes

1 655 women were ineligible or declined recruitment to PROSPECT after screening: No prolapse / changed mind about needing surgery (117); Removed from waiting list / unfit for surgery (45); Unable to give informed consent (32); Unable to complete questionnaires (16); Not interested in participation in study / unknown (413); Other reasons for non-recruitment *(including 'psychological or family problems', 'not clinically or medically suitable to take part in a research study' and 'consultant wished to decide procedure')* (32).

2 241 women declined randomisation:
'Clinical decision' includes 'wanted to use mesh', 'did not want to use mesh' and 'other clinical reason' (133);
'Participant decision' includes 'wanted mesh', 'did not want mesh' 'wanted surgeon to decide' and 'did not want to be randomised' (96)
'Other' reasons' include 'mesh unavailable', 'operating surgeon not trained in mesh inlays/kits', 'theatre time issues' and 'not recorded' (12)

3 Post randomisation exclusion: 1 woman had secondary prolapse surgery after consenting but prior to randomisation. She was followed up the cohort study (CC2).

4 56 randomised women were included in the standard repair arm, 52 in the synthetic mesh inlay arm and 46 in the synthetic mesh kit arm (total 154). 24 women in Stratum A were included in both the Mesh Inlay and Mesh Kit Trials, such that there were a total of 55 women in the standard repair arm of the Mesh Inlay Trial and 25 women in the standard repair arm of the Mesh Kit Trial. The numbers of participating women by individual strata are set out in Supplementary Figure 1.

5 Percentages shown represent the number of women as a proportion of those included in the analysis.

6 Other surgery includes women who did not have either an anterior or posterior repair, but did receive one or more of: tape for urinary incontinence, vaginal hysterectomy or suspension, cervical amputation, vault repair